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FORMULATION AND *IN VITRO* EVALUATION OF COPOLYMERIZED HYDROGEL BASED EMPAGLIFLOZIN MICROPARTICLES

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Abstract:

The aim of this work was to enhance the physical and chemical properties of natural polymers while simultaneously reducing production costs by graft copolymerization procedures involving the natural polymer guar gum and the synthetic polymer poly(acrylamide). The optimal hydrogel formulation was developed as microparticles, incorporating Empagliflozin and characterized by various criteria. A graft copolymer of guar gum-g-poly(acrylamide) was synthesized using a free radical polymerization method in a specifically built jacketed reaction vessel under a continuous flow of nitrogen. Ceric ammonium nitrate (CAN) was employed as the initiator for the reaction. The preparation conditions of microparticles were adjusted by evaluating the entrapment effectiveness percentage, particle size, swelling index under varying pH settings, and their release profiles. FTIR measurements support the development of grafted copolymers, whereas DSC experiments indicate a relatively enhanced heat stability of these copolymers. The pAAm-g-GG/sodium alginate microparticles exhibited a nearly spherical morphology, as demonstrated by the SEM analysis. The swelling index was shown to be highest for the formulation that contains more concentration of alginate in phosphate buffer at pH 6.8. The release of Empagliflozin was discovered to be regulated with increasing polyacrylamide and sodium alginate content in the microparticles, with a greater release noted in a pH 6.8 medium compared to pH 1.2. The in vitro kinetics of Empagliflozin release from the polymeric microparticle adhered to the zero-order kinetics model with mechanism of release as anomalous diffusion. Empagliflozin microparticles based on hydrogel were effectively synthesized with optimized batches of Guar gum-g-poly(acrylamide) and sodium alginate through free radical ionization methods. All characterization parameters met the acceptance standards.

Keywords: *Empagliflozin, Microparticles, Hydrogel, Guar gum, Acrylamide, Sodium alginate*

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INTRODUCTION:

The hydrogel-based drug delivery system is a highly promising innovative technique for the prolonged administration of pharmaceuticals. Hydrogels are three-dimensional network polymers that swell in aqueous solutions, becoming soft and rubber in their swelled condition, imitating biological tissue, with some exhibiting exceptional biocompatibility. Hydrogel systems exhibit significant stability under varying variables such as pH, ionic strength, temperature, and the fluctuating environment of the gastrointestinal tract, which differs from the stomach to the intestine [1]. Hydrogels derived from natural polymers, particularly polysaccharides, are extensively utilized due to their benefits over synthetic polymers, including non-toxicity, biocompatibility, biodegradability, abundant availability, and the ability to modify aqueous properties, thicken, emulsify, stabilize, encapsulate, swell, and form gels and films. However, they can be altered to mitigate certain disadvantages, such as unregulated hydration rates, microbiological contamination, and viscosity reduction during storage. Graft copolymerization is a simplified technique for altering the structure of natural polymers, enhancing their appeal as biomaterials in controlled release applications. [2]

Microparticles are defined as free-flowing entities composed of proteins, synthetic proteins, or biodegradable synthetic polymers, typically exhibiting a particle size within the micron range, and are capable of sustained drug release. Sodium alginate is a salt of alginic acid that can crosslink with other natural or synthetic polymers upon interaction with divalent or trivalent cations, a process known as ionic gelation. Alginate is a natural carbohydrate polymer frequently utilized in drug delivery systems due to its biodegradability, biocompatibility, and non-toxicity. Alginate is a linear polysaccharide derived from brown algae, with various proportions of 1,4-linked β-D-mannuronic acid and α-L-guluronic acid residues. Sodium alginate has been commercially utilized and studied because to its affordability and minimum processing demands. Alginate gelation takes place when divalent or trivalent cations (usually Ca^{2+}), interacts ionically with guluronic acid residues, resulting in formation of a three-dimensional network which is usually described by egg-box model. Alginate- Ca^{2+} has been widely investigated for oral and nasal drug-controlled release applications. So, calcium chloride can be used as a cross-linking agent for the preparation of microparticle in ionic gelation method [3, 4].

Type 2 diabetes mellitus (T2DM) is a common chronic metabolic condition necessitating lifelong care and continuous monitoring. Empagliflozin is a widely utilized SGLT2 inhibitor that regulates blood glucose levels by enhancing urine glucose excretion, while also providing cardiovascular and renal advantages. Medicine has significant solubility in water, thereby necessitating the development of a sustained release formulation to extend drug release, decrease administration frequency, and enhance patient compliance. This work concentrates on the development of Empagliflozin microparticles utilizing hydrogel for the successful control of Type 2 Diabetes Mellitus (T2DM). [5, 6]

MATERIAL AND METHODS:

Materials

Empagliflozin was acquired as a complimentary sample from Dr. Reddy's Laboratories, Hyderabad, India. Guar gum was obtained from the Girijan Cooperative Corporation in Hyderabad, India. Acrylamide was acquired from Nice Chemicals Pvt. Ltd., Mumbai, India. Calcium chloride ($CaCl_2$) was obtained from Central Drug House (P) Ltd., New Delhi, India. Acetone and potassium dihydrogen phosphate were procured from Sara Fine Chemicals, Baroda, India. All chemicals and reagents utilized in the investigation were of analytical laboratory quality. Laboratory-prepared double-distilled water was utilized throughout the research.

Synthesis of graft copolymer of guar gum-Acrylamide

The graft copolymerization was carried out in a specially designed jacketed reaction vessel having an inlet and outlet port. The inlet port related to the nitrogen gas supplied from the nitrogen cylinder (AR grade). The grafted copolymer of guar gum and Acrylamide was prepared by free radical polymerization technique. Specified amount of guar gum was dissolved in 75-150 ml of water and soaked overnight under stirring in a 250 ml round bottom flask for complete hydration. Then specified amount of Acrylamide was dissolved in 20ml of water and added to GG solution and mixed uniformly for 1 hour and the mixture was transferred to reaction vessel. To this solution, ceric Ammonium nitrate (CAN) was added in various concentrations to optimise the formulation and to get better yield. Polymerization was carried out at 60 ^{0}C with a continuous purging of nitrogen gas for 6 hours in a magnetic stirrer at 100 rpm. After complete polymerization, enough acetone was added to precipitate the grafted co-polymer. Then the grafted polymer was filtered and dried in hot air oven at 40 ^{0}C for 24 hours [7-10].

The % yield was calculated as
Percentage yield = (mass of the co-polymer after drying/ mass of the total polymer) × 100

The graft co-polymerization method was optimized for the optimum graft yield using different proportions of guar gum and polyacrylamide and using different concentration of initiator (CAN). The results are shown in table-1 indicating different proportions of guar gum and polyacrylamide with different concentrations of CAN and % yield of co-polymer.[11-12]

Table 1: Composition of polymers & initiator for different batches in copolymer (CP) synthesis.

Batch	Wt. of Guar gum (gm)	Wt. of AAm (gm)	Ratio of polymer (GG:AAm)	Concentration of CAN (M)	% Yield
CP_1	1	3	1:3	0.167	86%
CP_2	1	3	1:3	0.128	88%
CP_3	1	3	1:3	0.121	91%
CP_4	1	3	1:3	0.091	93%
CP_5	1	3	1:3	0.055	94%
CP_6	**1**	**3**	**1:3**	**0.036**	**99%**
CP_7	1	3	1:3	0.005	-
CP_8	1	2	1:2	0.036	81%
CP_9	1	1	1:1	0.036	72%
CP_{10}	2	1	2:1	0.036	64%
CP_{11}	3	1	3:1	0.036	52%
CP_{12}	1	4	1:4	0.036	83%

Preparation of pAAm-g-GG/Sodium alginate microparticles

Specified amounts of dried hydrogel were taken and crushed in a mortar and pestle using hot water till a uniform paste like mass was formed. Then specified amount of sodium alginate was mixed with 25ml of water and crushed properly to form a gel like mass and mixed with uniform paste like mass of hydrogel by trituration method. Then the paste like mass was put drop wise in 200ml of 0.054 M $CaCl_2$ solution from a syringe containing 0.1mm needle. Formed spongy globules were then filtered and washed with distilled water several times and blotted with soft filter paper and dried in a hot air oven at 40 ^{0}C for 24 hours. The different ratio of hydrogel and sodium alginate used are shown in table-2. [13-14]

Loading of Empagliflozin in microparticles

Microparticles prepared from various formulations were infused with the medication by immersion in an aqueous solution comprising 10% (w/v) of Empagliflozin. Soaking was conducted for approximately 24 hours to achieve perfect equilibrium. The formulations were filtered, and the drug solution adhering to the surface was eliminated using washing and blotting with soft filter paper. The samples were air-dried and subsequently stored in a desiccator for future use.

The drug was also included during the production of microparticles using the trituration process. The requisite quantity of the drug was combined with a minimal amount of distilled water, and the resulting drug solution was incorporated into the semisolid mass generated by the trituration of hydrogel and sodium alginate. [15-16]

Table-2: Composition of different formulations of Empagliflozin microparticles (EMM)

Formulations	Ratio of Polymers in Hydrogel (GG:AAm)	Ratio of Hydrogel : SA in microparticles	% Yield
EMM $_1$	1:3	3:1	97.5%
EMM $_2$	1:3	2:1	98.4%
EMM $_3$	1:3	1:1	97.6%
EMM $_4$	1:3	1:2	96.5%
EMM $_5$	**1:3**	**1:3**	98.2%
EMM $_6$	1:2	1:3	96.4%
EMM $_7$	1:1	1:3	97.5%
EMM $_8$	2:1	1:3	95.7%
EMM $_9$	3:1	1:3	94.4%

EMM $_{10}$	1:4	1:3	90.6%

CHARACTERIZATION OF pAAm-g-GG HYDROGEL AND DRUG-LOADED MICROPARTICLE

Drug-polymer compatibility study by Fourier Transform Infrared (FTIR) spectroscopy

Guar gum grafted copolymer and the cross-linked drug-loaded microparticles, along with individual polymers, were analysed by FTIR spectroscopy to confirm grafting and cross-linked reactions. The polymer samples were crushed with potassium bromide to make pellets. Spectra were taken on a Perkin Elmer Paragon 500 FTIR spectrophotometer in a range of 400-4000 cm^{-1}. [17-18]

Differential Scanning Calorimetry (DSC) Study

DSC is a thermo-analytical method in which the amount of heat needed to increase the temperature of a sample as a function of temperature is measured. Throughout the experiment, the temperature is maintained almost the same for the sample and the reference. It is a method in which it measures the physical properties of the sample, i.e. when the sample is cooled or heated, it measures the energy absorbed or released. During heating or cooling, the sample may undergo one or more phases. The DSC studies were carried out for pure drug and optimised formulation. The sample was heated from room temperature to 600 ^{0}C at a heating rate of 10 ^{0}C per min. The obtained peaks were compared, which usually indicated the melting point of the sample. [19-20]

Particle shape and surface morphology

Scanning Electron Microscopy (SEM) was employed to analyze the surface morphology of microparticles. An SEM investigation entails employing an electron beam to examine the nanoscale surface topography, dimensions, morphology, and elemental content of pharmaceutical formulations and raw materials. It surpasses the resolution constraints of conventional optical microscopes. Samples were made by applying lyophilized microparticles onto double-sided sticky tape affixed to an aluminum stub. A gold coating, approximately 300 angstroms thick, was applied using a sputter coater. Samples were analyzed, and photomicrographs were captured using a scanning electron microscope (LEO 435 VP, Eindhoven, Netherlands) at an acceleration voltage of 30 kV. The SEM imaging was conducted at the Indian Institute of Science Education and Research (IISER), Bhopal, Madhya Pradesh, India.[21-22]

Swelling Studies

Equilibrium water uptake of the cross-linked drug loaded microparticles were measured by measuring the extent of swelling of the matrixes in phosphate buffer pH 6.8. To establish compete equilibrium, the samples were allowed to swell for 24 hours. An electronic microbalance was used to weigh the enlarged microparticles to an accuracy of 0.01 mg after the extra liquid droplets that had stuck to the surface were blotted off using filter paper. After that, the hydrogel microparticles were dried for five hours at 60 degrees Celsius in an oven until the samples' dried mass remained unchanged. [23–24] The percentage of equilibrium water uptake was computed as follows:
(Mass of swollen microparticles – Mass of dry microparticles / Mass of dry microparticles) × 100

Estimation of Drug Entrapment Efficiency of microparticles

The drug entrapment efficiency of prepared microparticles was estimated by mechanically crushing the microparticles in presence of phosphate buffer pH 6.8 as the hydrogel microparticles can't be dissolved completely in organic solvents or acids. The solution was then gently heated for 2 hours to extract the drugs completely and filtered to analyze the amount of Empagliflozin entrapped by using a UV-Visible spectrophotometer at 224 nm.[25-26]

***In Vitro* drug release study**

A USP-I rotating basket dissolution equipment was used to perform the in vitro drug release from the pAAm-g-GG/Sodium alginate hydrogel microparticles at 37 °C and 100 rpm. After two-step dissolving conditions, the pH of the dissolution medium was changed at various intervals to maintain an accurate simulation of gastrointestinal (GIT) conditions. The first two hours of dissolution were done in 900 ml of HCl buffer pH 1.2, and the remaining time was spent in 900 ml of phosphate buffer pH 6.8 at regular intervals. The aliquots were taken out and tested for drug using a UV-visible spectrophotometer at 224 nm in order to replicate the physiological conditions of the GIT. An equivalent volume of brand-new dissolution medium was added to the dissolution medium following each sampling. Every dissolution study was conducted three times [27, 28].

Kinetics of release profile

To study the release kinetics, data obtained from *in vitro* drug release studies were plotted in various kinetic models.

Zero-order kinetics was plotted as cumulative percentage amount of drug release vs. time, and the equation is represented as follows.
$C = K_0 t$, where C = Cumulative drug release at time t.
K_0 = Zero-order rate constant
First order kinetics was plotted as log cumulative percentage amount of drug release vs. time and the equation is represented as follows.
$\log C = \log C_0 – K_1t/2.303$ where C = Amount of drug remained at time t
C_O = Initial amount of drug
K_1t = First order rate constant
Higuchi kinetics was plotted as cumulative percentage amount of drug release vs. square root of time and the equation is represented as follows.

$Q = K_H\ t1/2$
Q = Cumulative percentage drug release at time t.
In Korse-Meyer Peppas kinetic model graph is plotted between logarithms of cumulative drug release vs. logarithm of time. The equation is represented as following equation:

$F = Mt/ M\alpha = K_m t_n$
Where Mt is the drug released at time t, Mα is the total amount of drug in dosage form, F is the fraction of drug release at time t, Km is a constant dependent on geometry of dosage form, 'n' is the diffusion exponent indicating mechanism of drug release. [24, 29]

Stability Studies
In these studies, stability testing was carried out over a period of up to 90 days, i.e.,3 months, for selected microparticle formulations. This formulation, which was selected, had been examined for the *in vitro* release study and physical appearance. For accelerated testing, the storage condition was maintained at 40°C±2°C and 75%±5% RH and the results of appearance and entrapment efficiency were compared with fresh formulations. [26, 30]

RESULTS AND DISCUSSION:

Optimization of graft co-polymerization techniques
This study intended to achieve graft copolymerization of GG with Acrylamide by a Ce(IV) catalyzed free radical reaction. The chelate complex produced between the –OH group of GG decomposes to produce a free radical site, enabling grafting to occur at the active site of GG with the acrylamide monomer. The graft copolymerization process was adjusted by adjusting the concentration and ratio of the polymer, comparing the yield from batch to batch. to concentrations beyond 0.1276 M, the resultant hydrogel exhibited a sticky consistency and settled to the bottom, resulting in reduced yield. Utilizing concentrations ranging from 0.1276 M to 0.0182 M resulted in the formation of a non-sticky hydrogel that floated on the surface. The greatest yield was achieved at a polymer ratio of 1:3 (GG:pAAm) with a CAN concentration of 0.0364 M.

Formulations of GG-pAAm hydrogel/sodium alginate microparticles
Hydrogel was prepared using various ratios of GG and pAAm with an optimized concentration of CAN. Various ratios of hydrogel and sodium alginate were utilized for the production of microparticles. It was noted that when the hydrogel:SA ratio was 3:1, the resulting microparticles failed to maintain their spherical shape post-drying. Increasing the surface area ratio allows for the retention of the spherical morphology of microparticles, with optimal results achieved at a hydrogel to surface area ratio of 1:3, when the ratio of GG to pAAm in the hydrogel is similarly 1:3.

FTIR characterization of graft copolymer and drug polymer compatibility study in microparticles
To ascertain the compatibilities of the drug and polymers utilized in various formulations, FTIR spectra of the pure drug, polymers, and the physical mixture of the drug and polymer were conducted. Upon comparison of the spectra of Empagliflozin with the microparticles of the improved formulation, the distinct peaks observed in Empagliflozin at 3324 cm-1, 3522 cm-1, and 2899.9 cm-1 are also present in the microparticles of the optimized formulation. The aforementioned investigations revealed that the principal peaks remained unchanged, indicating an absence of interaction between the medication and the various components utilized in the formation of distinct microparticle formulations. Consequently, the medication and excipients exhibit compatibility, enabling the formation of stable formulations under investigation. The FTIR spectra of Empagliflozin and the microparticles of the improved formulation were acquired, as depicted in Figure 1.

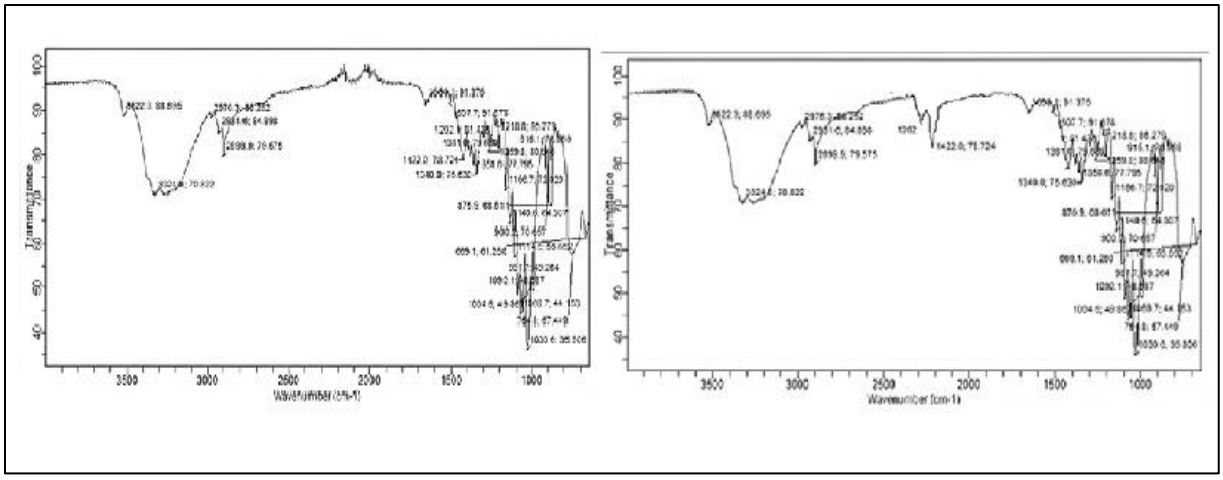

Fig. 1: Comparative studies of FTIR spectra of pure Empagliflozin, and Microparticles.

DSC Study

The DSC thermogram of the improved formulation of Empagliflozin microparticles was acquired to assess potential thermal interactions between the medication and the polymer. This study presents the endothermic peaks observed in both the pure medication and the optimized formulation of microparticles. The endothermic peak was recorded at 152.22 °C for both Empagliflozin and the improved formulation of microparticles. The DSC studies indicated that the formulation is thermodynamically stable, as it necessitated slightly more heat than the pure drug due to the presence of various excipients with the drug. No transition of peaks from endothermic to exothermic was observed. Figure 2 displays the DSC thermograms for the pure medication and the improved formulation of microparticles.

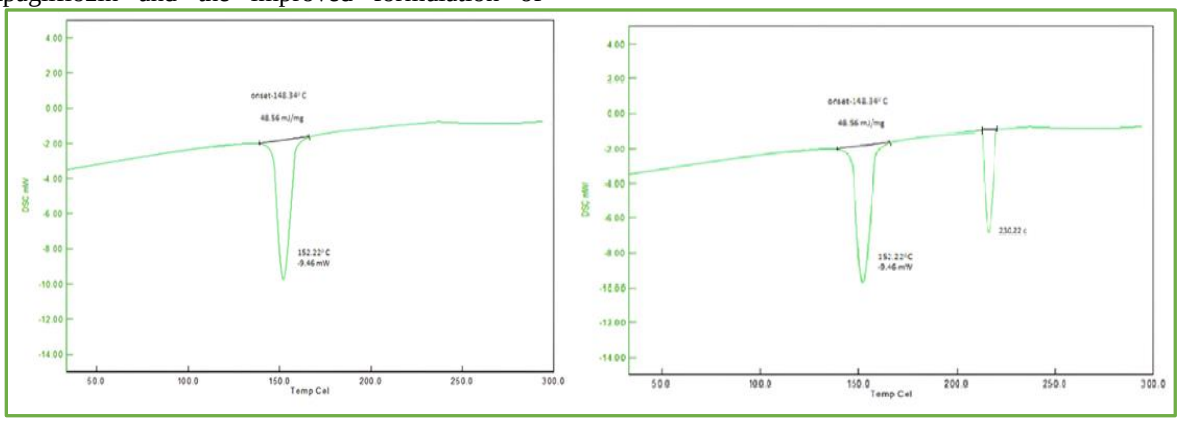

Fig. 2: DSC thermogram of pure Empagliflozin and microparticles.

Particle shape and surface morphology

Scanning electron microscopy (SEM) investigation indicated that the optimized microparticle formulation exhibited a spherical shape and a smooth surface, as shown in Figure 3. Particles have remarkable uniformity and consistency in their size. Circular with uninterrupted, non-aggregated, and impermeable surfaces. The precise dimensions of the microparticle varied from 8 µm to 19 µm.

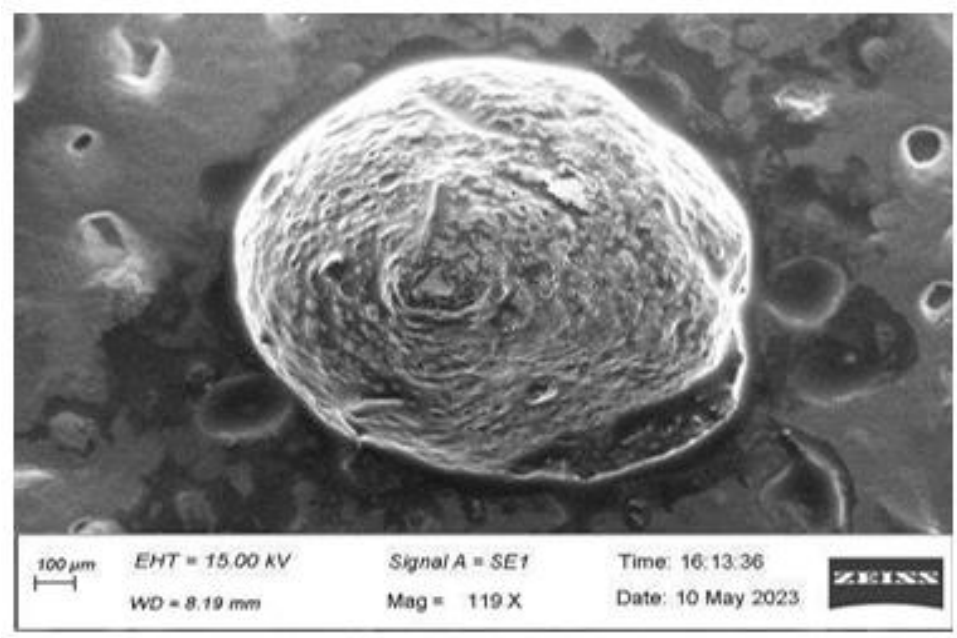

Fig. 3: SEM photomicrograph of Empagliflozin loaded microparticles

Drug entrapment efficiency

Drug was incorporated into the microparticles during the preparation process, and the entrapment efficiency of different formulations was evaluated. The prepared microparticles showed high drug entrapment efficiency ranging from 90.68% to 98.46% for various batches. The high entrapment efficiency may be attributed to the effective polymer network formed by the hydrogel system, which efficiently retained the drug within the microparticles. Among all formulations, EMM_{10} exhibited the highest drug entrapment efficiency of 98.46%, indicating efficient drug incorporation and uniform distribution within the polymeric matrix. The results of drug entrapment efficiency are represented in the corresponding histogram. Figure 3 showing percentage drug content of different formulations.

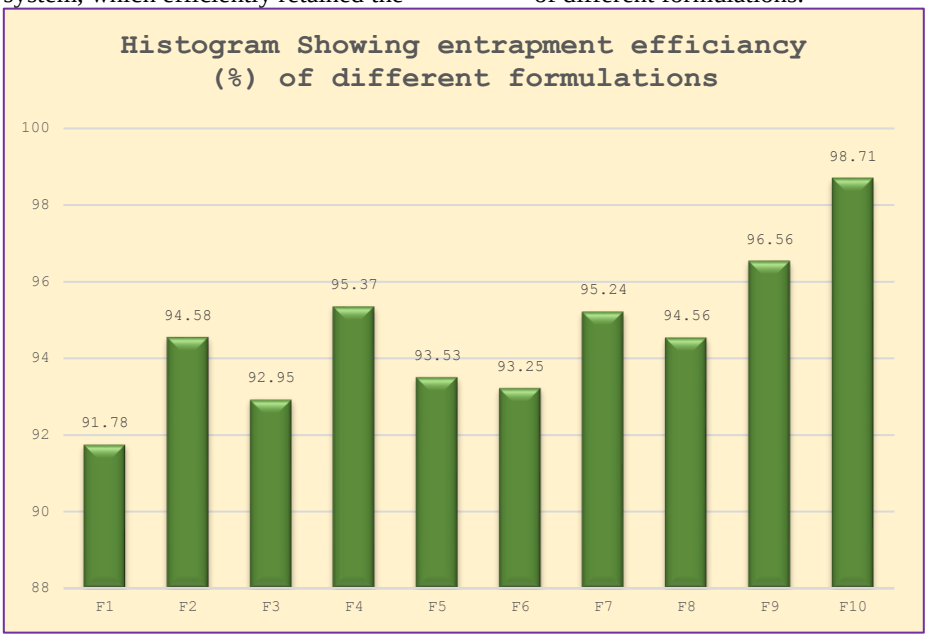

Fig. 4: Comparison of % drug entrapment efficiency of prepared Empagliflozin microparticles

Swelling studies

Swelling studies of the prepared Empagliflozin microparticles were carried out in phosphate buffer pH 6.8 to evaluate the fluid uptake behaviour of the hydrogel system. The swelling ability of the microparticles increased gradually with time due to absorption of dissolution medium into the polymeric network. The swelling index varied among different formulations depending on the polymer concentration and composition. Among all formulations, EMM_{10} showed a maximum swelling index of 98±1.6 at the end of 10 hours, indicating better hydration and controlled swelling behaviour. The swelling profiles of all formulations are represented in the corresponding histogram.

***In Vitro* drug release study**

To study the release behaviour of Empagliflozin from the formulated microparticles under gastrointestinal conditions, *in vitro* release of Empagliflozin from the formulated microparticles was performed in pH progressive media using HCl buffer pH 1.2 for first 2 hours followed by phosphate buffer pH 6.8 for remaining period. The rate and extent of drug release were dependent on the concentration and ratio of polymers in the formulations. An increase in concentration of sodium alginate showed a faster drug release while increasing the concentration of ethyl cellulose retarded the release due to its hydrophobic nature. Among all the formulations, EMM_{10} showed a sustained and controlled release profile of the drug up to 12 h with 99.8% cumulative drug release. On the contrary, formulations with low polymer concentration exhibited comparatively faster drug release. The results suggest the effective control of the release of Empagliflozin from the hydrogel microparticles by an optimum combination of polymers. The *in vitro* drug release study of Empagliflozin loaded microparticles is represented in figure 4.

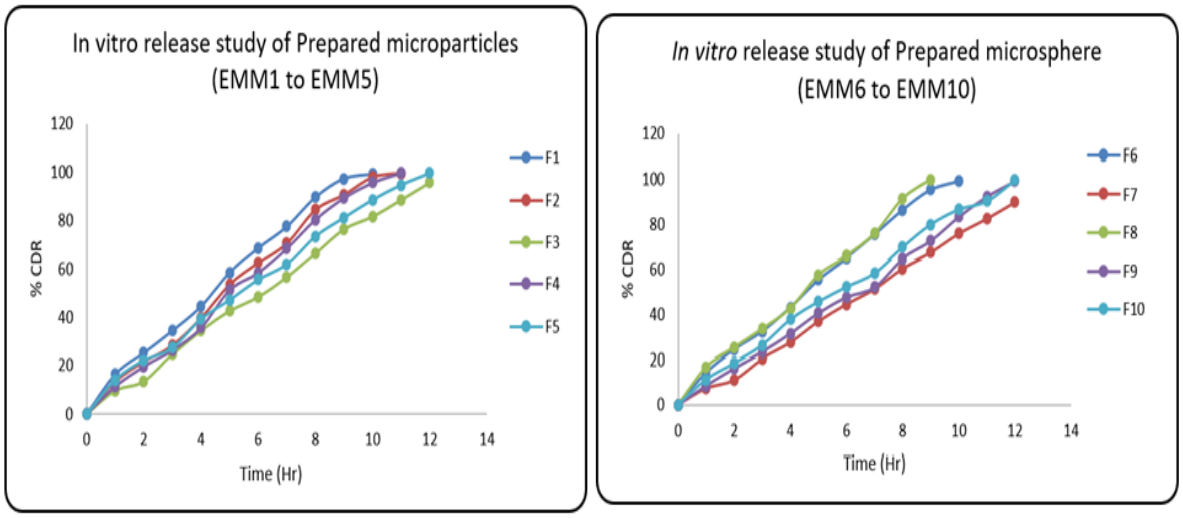

Fig. 5: Showing *in vitro* drug release study of Empagliflozin loaded microparticles.

***In vitro* drug release kinetic mechanism**

In vitro release data of optimised formulation EMM_{10} were fitted to various kinetic models such as zero order, first order, Higuchi, and Korsmeyer–Peppas models to identify the mechanism of drug release from the prepared Empagliflozin microparticles. The regression coefficient (R^2) values of all models were compared to find the best fit release pattern. The regression coefficient was found to be maximum for the optimised formulation with zero order model (R^2 = 0.9945) among the different models indicating controlled and concentration independent drug release profile. The release exponent obtained from Peppas plot (n = 0.8930) indicated that the drug release followed anomalous diffusion mechanism which involves both diffusion and polymer erosion. Figure 5 indicates plots of kinetic studies.

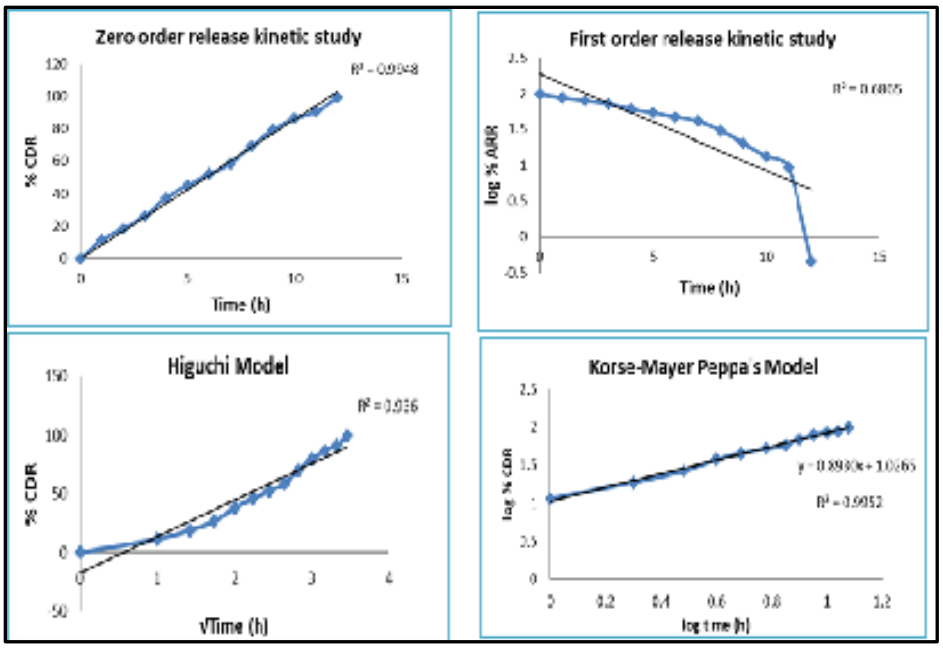

Fig. 6: Showing *in-vitro* drug release kinetic studies.

Stability studies

The optimised empagliflozin microparticles were subjected to accelerated stability studies for three months at 40°C ± 2°C / 75% ± 5% RH as per ICH guidelines. The drug content of the formulations showed only a slight change after storage while the physical appearance showed no significant change. The overall results suggested that the microparticles prepared were chemically and physically stable under accelerated storage conditions.

CONCLUSION:

The ionotropic gelation method was effectively utilized to fabricate empagliflozin-loaded hydrogel microparticles utilizing sodium alginate, ethyl cellulose, and other polymers. The sustained drug release profile was achieved by formulating several compositions by alterations in polymer concentration and ratios. The produced microparticles demonstrated a high drug entrapment efficiency between 90.68% and 98.46%, indicating efficient drug integration inside the polymeric matrix. FTIR analyses indicated no substantial interaction between Empagliflozin and the polymers in the formulation. Swelling experiments demonstrated a progressive absorption of fluid by the microparticles, which influenced the drug release kinetics. The swelling index varies for each formulation according to the polymer concentration and composition. *In vitro* drug release tests were conducted in HCl buffer at pH 1.2 and phosphate buffer at pH 6.8. The results indicated that formulations with a higher concentration of ethyl cellulose exhibited prolonged drug release owing to its hydrophobic characteristics. The EMM*10* formulation demonstrated superiority across all formulations, exhibiting a regulated release profile that virtually achieves complete drug release within 12 hours. The kinetic release studies indicated that the improved formulation adhered to zero-order kinetics, characterized by an anomalous diffusion mechanism coupled with erosion that encompassed both diffusion and erosion processes. Stability investigations indicated that the optimized formulation remained stable under accelerated storage settings for three months, exhibiting no significant alterations in drug content or physical appearance. The formulated Empagliflozin encapsulated in hydrogel microparticles presents a promising sustained-release medication delivery strategy for the successful management of Type 2 Diabetes Mellitus.

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REFERENCES:

1. Gwen MJ., Joseph RR., Banker GS and Rhodes CT, (editors). Modern pharmaceutics. 3rd ed., Morcel Dekker. Inc, 1996, 575.
2. Chein YW., Novel drug delivery system. 2nd ed. Morcel Dekker. Inc, 1997, 1-42.
3. Goodman and Gillman's, The Pharmacological Basis of Therapeutics, 11th ed. Laurence L. Brunton, John S. Lazo, 1635-1638.
4. www. Medicines.org.uk/emc/browsedocuments
5. Aulton ME. Wells TI., Pharmaceutics: The Science of Dosage Form Design, London, England: Churchill Livingstone: 1988: 185-189.
6. X. QU, A. Wirsen, A.C Albertsson, Novel P^{H}-sensitive chitosan hydrogel: swelling behaviour and states of water, polymer 41 (2000) 4589-4598.
7. Narayan B; Jonathan G; Miqin Z; chitosan based hydrogels for controlled localised drug delivery. Adv. Drug Delivery Re 2010, 62, 83-99.
8. Tejraj M. Aminabhavi; *et al* water transport and drug release study from cross-linked polyacrylamide grafted guar gum hydrogel microsperes for the controlled release application, Euro. Jour. of Ph. And Bioph. 53 (2002) 87-98.
9. P. Sunny Gils, et al; controlled release of Doxofylline from Biopolymer based Hydrogels; Am.Jour. of Biomed. Sc. 2010, 2(4), 373-383.
10. Baljit S., Nirmala, C.; Diatary fiber Psyllium based hydrogels for use insulin delivery. Int. J. Diabet. Melt. 2010, 2, 32-37.
11. T.M Aminavi, G.V. Patil, S.F. Harlapur; R.H. Balundgi; A reviewed on sustained release of cardiovascular drugs through Hydroxy Propyl Methyl Cellulose and sodium carboxymethyl cellulose polymers, Des.Monom. Polym.1(1998) 347-372.
12. B. Gander, V.Beltrami, R. Gurny. et.al, Effects of the method of drug incorporation and the monolith on drug release from cross-linked polymers. Int. J. Pharm. 58(1990) 63-71.
13. Carstensen, J.T.; C.T. Rhodes Drug stability; Principles and practicle; Markel Dekkar: New York; 2000.
14. Hadjioannu T.P.,et.al, Quantitative Calculations in Pharmaceutical Practice and Research, New York: VCH Publishers Inc., 1993, 345-348.
15. Dos Santos, K.S.C.K.; Coelho, et al synthesis and characterization of members obtained by graft copolymerization of 2-Hydroxyethyl methycrylate and acrylic acid onto chitosan. Int. J. Pharm 2006, 310, 37-45.
16. Panda N, Panda KC, Reddy AV, Reddy GV. Process optimization, formulation and evaluation of hydrogel {guargum-g-poly (acrylamide)} based doxofylline microbeads. Asian J Pharm Clin Res. 2014;7(3):60-5.
17. Kumar AR. Aeila AS. Sustained release matrix type drug delivery system: An overview. World J Pharma Pharm Sci. 2019; Oct 24; 8(12): 470-80. DOI: 10.20959/wjpps20201-15241.
18. Saxena AK. Sharma A. Verma N. Microspheres as therapeutically effective multiparticulate drug delivery system: A systemic review. Research Journal of Pharmacy and Technology. 2021; 14(6): 3461-70.
19. Vinod R. Kumar PA. Yadav AS. Rao BS. Kulkarni SV. Formulation and Evaluation of Controlled Release Microspheres of Zidovudine. Research Journal of Pharmaceutical Dosage Forms and Technology. 2010; 2(1): 96-9.
20. Kumbhar DM. Mali KK. Dias RJ. Havaldar VD. Ghorpade VS. Salunkhe NH. Formulation and development of ethyl cellulose coated pectin based capecitabine loaded microspheres for colorectal cancer. Research Journal of Pharmaceutical Dosage Forms and Technology. 2016; 8(4): 261-8.
21. Chandarsekaran N. Balamurugan M. Formulation, Characterization and In-vitro Evaluation of Abacavir Sulphate Loaded Microspheres. Research Journal of Pharmacy and Technology. 2013; 6(7): 731-5.
22. Patel NR. Patel DA. Bharadia PDet al. Microsphere as a novel drug delivery. International Journal of Pharmacy and Life Sciences. 2011; Aug 1; 2(8): 992-997.
23. Patil UK. Sahu R. Yadav SK. Formulation and Evaluation of Controlled Release Microspheres Containing Metformin Hydrochloride. Research Journal of Pharmacy and Technology. 2009; 2(1): 176-9.
24. Ratnaparkhi MP, Gupta jyoti P. Sustained release oral drug delivery systeman overview. International Journal of Pharma Research and Review. 2013; 2(3): 11-21.
25. Bose S. Kaur A. Sharma SK. A review on advances of sustained release drug delivery system. Int. Res. J. Pharm. 2013; 4: 1-5.
26. Gavini V. Murthy MS. Kumar PK. Radhika DL. Formulation and in-vitro evaluation of mucoadhesive microspheres loaded with stavudine using hydrophilic macromolecular polymers. Research Journal of Pharmaceutical Dosage Forms and Technology. 2014; 6(2): 99-104.

27. Talokar SS. Vakhariya RR. Formulation and evaluation of lomefloxacin microspheres. Research Journal of Pharmaceutical Dosage Forms and Technology. 2017; 9(1): 1-5.
28. Nighute AB. Bhise SB. Preparation and evaluation of rifabutin loaded polymeric microspheres. Research Journal of Pharmacy and Technology. 2009; 2(2): 371-4.
29. Ahmed TA. Aljaeid BM. Preparation, characterization, and potential application of chitosan, chitosan derivatives, and chitosan metal nanoparticles in pharmaceutical drug delivery. Drug Design, Development and Therapy. 2016; Jan 28: 483-507.
30. Denkbaş EB. Seyyal M. Pişkin E. Implantable 5-fluorouracil loaded chitosan scaffolds prepared by wet spinning. Journal of Membrane Science. 2000; Jul 1; 172(1-2): 33-8. https://doi.org/10.1016/S0376-7388(00)00314-8.